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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SCHNIZER, HOLLY G	
ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 10/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/455,978	ALAM ET AL.	
	Examiner	Art Unit	
	Holly Schnizer	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6,11,16,48,49,51-54 and 66-82* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,11,48,49,51-54 and 66-82* is/are rejected.

7)☒ Claim(s) *6 and 16* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 1, 6, 11, 16, 48-49, 51-54, 66-82 are pending and have been considered in this Office Action.

Rejections Withdrawn

The rejection of Claim 64 is rejected under 35 U.S.C. 112, second paragraph is withdrawn in light of its cancellation.

The rejection of Claims 1-6 under 35 U.S.C. 102(b) as being anticipated by Zhang et al. (Proc. Natl. Acad. Sci (1996) Vol. 93, pp. 4649-4654 ; ref. 16 in IDS of Paper No. 4) is withdrawn in light of the amendments and the Declaration of Maqsudul Alam under 37 C.F.R. 1.132 which states that Alam is a coauthor of the Zhang et al. reference and that non of the partially purified H. salinarium signal transducer proteins disclosed in Zhang et al. were complexed with a heme molecule (see paragraph 7).

The rejection of Claims 1, 3-5, 11, 13-15, and 64 under 35 U.S.C. 102(b) as being anticipated by Grinstaff et al. (U.S. Patent No. 5,635,207) is withdrawn in light of the amendments.

The rejection of Claims 1, 3-5, 11, 13-15, and 64 under 35 U.S.C. 102(b) as being anticipated by Sugimoto et al. (Biophysical Journal (Nov. 1998) 75: 2188-2194) is withdrawn in light of the amendments.

The rejection of Claims 1, 3-5, 11, 13-15, and 64 under 35 U.S.C. 102(b) as being anticipated by Zhao et al. (J. Biol. Chem. (Sept. 1995) 270(35): 20763-20774) is withdrawn in light of the amendments.

The rejection of Claims 1-6 and 66-67 under 35 U.S.C. 103(a) as being unpatentable over Zhang et al. (Proc. Natl. Acad. Sci (1996) Vol. 93, pp. 4649-4654 ; ref. 16 in IDS of Paper No. 4). In view of Yao and Spudich (Proc. Natl. Acad. Sci. (1992) 89: 11915-11919) and Yao et al. (J. Bacteriol. (1994) 176(22): 6931-6935) is withdrawn in light of the amendments.

The rejection of Claims 1-5 and 11-15, and 64-67 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in lieu of a modified rejection addressing the amended claims.

New Rejections Necessitated by Amendment

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 11, 66-68, 70, 73-76, and 81-82 are rejected under 35 U.S.C. 102(b) as being anticipated by Gong et al. (Proc. Natl. Acad. Sci. (Dec. 1998) 95: 15177-15182).

Gong et al. teach the recombinant expression and purification of FixL from B. japonicum. The FixL protein contains a heme binding domain and appears to bind oxygen reversibly and with low affinity (see Table 2 and compare binding constant with wild-type and mutant myoglobins). The FixL sequence contains a heme binding domain at the N-terminus and a aerotaxis signaling domain at the C-terminus and is about 50kDa(p. 15177, Col. 2, first paragraph). The FixL protein has 2 alpha helices which is considered to be a plurality (therefore it meets the limitations of claim 68; see Fig. 1 of Gong et al.). The heme binding protein of Gong et al. is bound to heme (an Fe-porphyrin;). Absent evidence of a component in the claimed blood substitute that is not present in the composition of Gong et al., the Gong et al. composition containing the FixL protein is considered patentably indistinguishable from the blood substitute compositions of Claims 11, 81, and 82. Thus, the claims are anticipated over the prior art.

Claims 1, 11, 66-68, 70, 73-76, and 81-82 are rejected under 35 U.S.C. 102(b) as being anticipated by Monson et al. (Proc. Natl. Acad. Sci. (1992) 89: 4280-4284).

Monson et al. teach the recombinant production of FixL from Rhizobium meliloti (Materials and Methods). The FixL protein disclosed in Monson et al. is considered to bind oxygen reversibly and with "low affinity" (p. 4280, Col. 2, 2nd paragraph). The FixL protein has a heme binding domain at the N-terminus and an aerotaxis signaling domain at the C-terminus (p. 4282, Col. 2, last paragraph). The purified fixL protein is complexed with heme (an Fe-porphyrin; Fig. 2 and p. 4282. Col. 1, Heme analysis). The heme binding domain of FixL contains 4 alpha helices which is considered a

plurality (p. 4280, Col. 2, 3rd paragraph). The complex disclosed in Monson et al. is 55 kDa, which is considered "about 50 kDa" (Fig. 1B). Absent evidence of a component in the claimed blood substitute that is not present in the composition of Monson et al., the Monson et al. composition containing the FixL protein is considered patentably indistinguishable from the blood substitute compositions of Claims 11, 81, and 82.

The examiner notes the spectral analysis of FixL and FixLN disclosed in Monson et al. in Figure 4C as compared to present Claims 77 and 78. These claims have not been rejected over Monson et al. since they recite the absorption at specific wavelengths rather than reciting "about" a particular wavelength. Therefore, while the wavelengths recorded in Monson et al. are close to the values of the claims, they are not exactly the same as recited in the claims and therefore Monson et al. does not anticipate claims 77 and 78.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 11, 48-49, 51-54, 66-82 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Specification does not provide a structure-function relationship

The complex: Claims 1, 11, and 66-82:

The present claims are drawn to proteins that have a specified activity (heme binding and reversible and low affinity oxygen binding and aerotaxis signaling) and no structure (claims 1, 11, 66-70 and 73-82) or minimal structure (a heme binding domain that has at least 20% identity to the sequence of SEQ ID NO:76 or a aerotaxis signaling domain with at least 30% identity to SEQ ID NO:79). However, the Specification only discloses the sequences of two proteins (only discloses two species) with such activity and does not provide any information about what modifications to the sequence of SEQ ID NO:76 or 79 can be made without eliminating the specified activities. The disclosure of two species is not considered sufficient to describe the genus of complexes claimed. What characteristics of SEQ ID NO:76 allow a protein to reversibly bind oxygen with low affinity or to be "salt-tolerant"? What characteristics of SEQ ID NO:79 in the context of the whole protein allow it to respond to the heme binding domain and produce a signal (binding or phosphorylation). The Specification is silent with regard to this information. Thus, with the Specification in hand, one of skill in the art would not be able to recognize what sequences would have heme binding activity and especially what protein sequences would have the coordinated heme binding and signaling activity that allows it to be a biological sensor. The written description requirement may be satisfied through disclosure of function and minimal structure when there is a well-established correlation between structure and function. However, without such correlation, the capability to recognize or understand the structure from mere recitation of function and

minimal structure is highly unlikely and does not satisfy the written description requirements.

The chimeric protein: Claims 48-49 and 51-54

Claims 48-49 and 51-54 are drawn to chimeric proteins comprising the any heme binding domain of an isolated heme binding bacterial protein and any heterologous signaling domain. The Specification does not provide any species that would be representative of this genus and does not provide guidance as to what signaling domains were contemplated for combining with what specific heme binding domains. While heme binding domains and signaling domains are known, one of skill in the art would not have recognized from the present Specification what heme binding domains and signaling domains could be combined in the chimeric protein to make a functional protein that would bind oxygen and activate the signaling domain. The mechanism of conformational change upon oxygen binding to the heme domain that would successfully activate the signaling domain was not known. Thus, one of skill in the art would not know which or how much of the sequence of a heme binding domain is necessary to produce such a conformational change that would activate the signaling domain nor how much of the signaling domain was required to receive such a signal from the heme binding domain.

Applicants argue that the specification identifies regions within the heme binding domain that are conserved among globin-type proteins. Upon review of the Specification, it appears that the Specification discloses the manual alignment of the two oxygen sensors disclosed with sperm whale myoglobin in an effort to find a minimal

length of protein containing a "myoglobin signature motif" and see how many myoglobin proteins this sequence would recognize in the database. However, such a search does not define the structural characteristics of the protein that allow it to bind oxygen through its heme binding domain and change conformation to activate the signaling domain. Thus, one of ordinary skill in the art would not be able to recognize what sequences or tertiary structures would produce a complex that would have the claimed functions or a functional chimeric protein.

The Specification does not set forth the invention in terms of distinguishing identifying characteristics that would allow one of skill in the art to recognize a sequence as being "bacterial" or from Archaea" or from "H. salinarum".

Applicants' response (August 7, 2003) to the prior art rejections states that "bacterial" is a property of the claimed protein. However, the Specification nor the response identifies what property of the protein characterizes it as being "bacterial" or from "Archaea", or from "H. salinarum". At the time of the invention, recombinant technology was routine and proteins were routinely modified and recombinantly produced from sources different from the source of the originating protein. Thus, if a protein isolated from bacteria were changed by one amino acid, would it still be considered "bacterial"? If so, when does the protein cease to be considered "bacterial"—how much modification is allowed to maintain its identity as "bacterial"? These questions are not answered in the present Specification or the art. Thus, one of skill in the art would not know what sequences of all of the sequences that have 20% identity to SEQ ID NO:76 would be considered "bacterial" sequences or sequences from

"Archaea" or from "H. salinarum". Thus, the claims do not meet the written description requirements.

Claim Objections

Claims 6 and 16 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusions

No claims are allowable. Claims 1, 11, 48-49, 51-54, and 66-82 are rejected. Claims 6 and 16 are objected to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (571) 272-0958. The examiner can normally be reached on Monday through Wednesday from 8 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Holly Schnizer
September 24, 2004

JON WEBER
SUPERVISORY PATENT EXAMINER